Remarks

Amended Claims

The invention is the discovery that contrary to all of the prior art, the claimed chemotherapeutic formulation of arsenic trioxide can be administered orally, with the same or better efficacy but surprisingly, with little or none of the side effects associated with administration intravenously.

The standard intravenous dosage is 10 mg/patient, with a range of 5-20 mg/patient administered over a period of one hour.

The standard oral dosage is equal to or less than 5 to 10 mg, with greater than 90% bioavailability. Due to the very slow absorption, there is a lower Cmax than with intravenous administration, and the peak levels are less than 50% of the intravenous peak levels. One would normally expect to see a lower efficacy with lower peak levels, but it has been demonstrated to be equally effective but with fewer side effects, especially with respect to the cardiotoxicity that is a dose limiting side effect associated with intravenous administration. The examiner's attention is drawn to the pharmacokinetics shown in Figure 1 comparing uptake following intravenous administration as compared to oral administration. His attention is also drawn to the evidence provided with the last response that clearly demonstrated the surprising pharmacokinetics associated with oral delivery. *See* in particular Exhibit 3 and the papers submitted with the Information Disclosure Statement mailed June 20, 2006.

These results could not have been predicted and are exactly the kind of evidence the Supreme Court was referring to in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), its recent decision relating to non-obviousness of claims over prior art.

The claims have been amended to reflect more accurately that the discovery is the oral administration of an effective amount of arsenic trioxide, rather than a method of making an oral arsenic trioxide solution. Support for the amendments to the claims is found, for example, at page 4, lines 28-30, page 5, lines 11-15, page 9, lines 19-21, page 18, line 1, and page 27, line 5. As noted above, the examples compare the bioavailability, plasma concentrations, uptake in tissues, and greater efficacy with fewer side effects of the oral preparation as compared with the intravenous administration. Support for the new claims is found at page 8. Claims 7, 8, 11-27, and 35-37 have been cancelled.

Rejections Under 35 U.S.C. § 102

Claims 1-3 and 7 were rejected under 35 U.S.C. § 102(b) as anticipated by WO 99/24029. Claims 1-3, 7 and 8 were rejected under 35 U.S.C. § 102(a) as anticipated by CN1370540. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As the examiner has correctly noted, the prior art discloses a composition which in theory could be administered orally. Intended use does not distinguish a composition from a known composition. Accordingly, the composition claims have been amended to define a dosage formulation for oral administration. Since there could be overlap through oral administration of

a solution suitable for administration intravenously, the claim has further been amended to define a dosage which is less than the dosage described in the prior art for intravenous administration, and further in dependent claims as 5-10 mg/day, or in the form of tablets or other dosage forms which are clearly not administerable intravenously.

Rejections Under 35 U.S.C. § 103

Claims 1-42 were rejected under 35 U.S.C. § 103(a) as obvious over WO 99/24029 and CN1370540. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The prior art does not recognize that arsenic trioxide can be orally administered in an effective amount with reduced side effects.

Indeed, CN137540 does not even mention oral administration of the drug, only conventional treatment of leukemia with arsenic trioxide.

WO 99/24029 at page 17 states that arsenic trioxide can be administered orally or topically or parenterally.

Topical administration is clearly impossible. Similarly, the boiler plate on page 16 provides that one could administer drug by inhalation, another impossibility. There is no disclosure of how much drug is given orally nor in what form it is given, other than to provide an 8-fold range of 2.5 to 40 mg. The dosage for intravenous treatment is stated to be greater than or less than 10 mg/day, with a preferred dose of 0.1 to about 5 mg/KG/day (page 17, lines 35-37).

WO 99/24029 fails to teach one skilled in the art to actually administer the formulation orally. It is well known in the art that bioavailability is generally considerably less orally than by intravenous administration. Moreover, it is common with administration of chemotherapeutic drugs to cause an extremely painful condition called mucositis, an inflammation of the mucosa. For these two reasons alone, one would not expect to be able to orally administer an effective dose, but with fewer side effects. One would expect to need a much larger dosage, not a lower dosage. There is no such teaching in WO 99/24029. ALL of the examples demonstrate intravenous administration and in the United States the drug is approved only for intravenous administration. Since oral administration is cheaper, easier, and safer, there is no question but that if those skilled in the art had believed such an option was available, they would have demonstrated its use. This is even more so considering the very dangerous side effects associated with intravenous administration (*see* enclosed package insert) which are avoided by oral administration, as demonstrated by the evidence that applicants have submitted. *See also* enclosed article in Blood, 1 September 2001, Vol. 98, No. 5, pp. 1632-1634.

Applicants provide pharmacokinetic differences that show that contrary to expectation, the arsenic trioxide formulation is orally bioavailable at substantially the same amount as the intravenously administered drug. This was even more surprising given the very low solubility and pH dependence of the arsenic trioxide in water.

In summary, the prior art neither discloses the compositions and methods as presently claimed, nor do they make obvious, in view of the differences in dosages, effective amounts, and

side effects, which could not have been predicted and were in fact taught away from by the prior art.

Should the examiner not feel the case is in condition for allowance, an interview with the undersigned would be greatly appreciated.

Allowance of claims 1-6, 9, 10, 28-34, and 38-44 is respectfully solicited.

Respectfully submitted.

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Date: June 15, 2007

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